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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,700	10/29/2003	Scott Pownall	029996-0306374	8349

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EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/697,700	POWNALL ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-51,53-59 and 61-87* is/are pending in the application.

4a) Of the above claim(s) *3,11,12,29-51,53 and 64-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-10, 13-16, 18-28, 54-59, 61-63 and 69-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/26/04; 12/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I (claims 1, 2, 4-10, 13-16, 18-28, 54-59, 61-63 and 69-87) in the reply filed on 3/29/07 is acknowledged. As well, applicants have selected for examination, a glycogen targeting subunit of PP-1 as a species of glycogenic enzymes. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim 3, 11, 12, 29-51, 53 and 64-68 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/29/07.

Priority

Applicants claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The instant application claims benefit of priority of provisional application 60/442,365, filed 10/29/02. The disclosure of the prior-filed application, US Provisional 60/442,365 fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The parent document does not provide support for induction of an amount of glycogen that will lead to morphological changes or apoptosis as recited in claims 4-6. As regards claims 9 and 10, 60/442365 teaches that enhancement for effecting glycogen deposition in cancer cells can occur in a variety of enzymes such as the glycogen targeting subunit of PP-1 wherein PP-1 is wild-type or mutant and can be overexpressed to induce a decrease in cell proliferation. However the instant claims are drawn to isoforms or family members of PP-1. 60/442365 teaches that the cell can be from stomach, liver, colon and prostate but does not include the full list of the cells as recited in claims 14, 15, 56, 59, 72 and 74 or use of ribozymes as recited in claim 19 or a vesicle associated with the vector as recited in claim 23. 60/442365 does not teach that the vector comprises a second protein as recited in claims 26-28 or that the method is directed towards treatment of cell proliferative disorders as a generic class of diseases or that exclude liver, muscle or brain cell disorders as recited in claims 54 and 57 or for treatment of tumors as recited in claims 62, 63 and 69-87. Therefore, the parent document does not provide support for these claims and a priority date of 10/29/03 will be attributed to claims 4-6, 9, 10, 14-16, 18, 19, 23, 26-28, 54-57, 62, 63 and 69-87.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 68, line 11-12. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claims 19, 54, 57, 62, 63 and 69-81 are drawn to non-elected subject matter. Claims 54, 57, 62, 63 and 69-81 include limitations that are drawn to non-elected subject matter in which an agent is used to increase the amount of intracellular glycogen. For claim 19, the role of "antisense polynucleotide, a small interfering RNA or a ribozyme" is intended to decrease expression of glycogenolytic enzymes. However, the elected claims are drawn to the contrary to gene products that increase synthesis or intracellular accumulation of glycogen. Therefore, "antisense polynucleotide, a small interfering RNA or a ribozyme" are non-elected subject matter.

Claims 15, 20, 24, 75, 80, 84, 85 and 87 are objected to because of the following informalities: in claim 15, each of the items listed in the Markush group should be preceded by an article such as --a-- or --an-- for grammatical accuracy.

Claim 24 recites, "expression of the gene product is conferred by a promoter". It would be remedial to recite --expression of the gene product is mediated by a promoter-- as the promoter doesn't actually confer but controls expression.

Claims 69-73 and 75-80 recite are dependent on claims 64 and 65, which do not explicitly recite that the subject comprises a tumor. For clarity it would be remedial to recite that the subject has a tumor.

Claim 75 recites, "tumor is haematopoetic". It would be remedial to recite --tumor is a haematopoetic tumor-- for grammatical accuracy.

In claim 76, an article for proper grammatical format --a-- must precede each of the tumor types.

Claims 84 and 87 include a colon prior to the Markush group, which should be deleted. As well, in claim 84 the "and" between (5-AZC) and 5-azacytidine should be deleted.

In claim 85, an article such as --a--or --an--for proper grammatical format must precede each of the cell types listed in the Markush group of cells.

Appropriate correction is required.

Claim 20 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 recites that a gene product is expressed in a cell and thus it can only be encoded by a polynucleotide as this is the only way to express a gene product. Hence, claim 20 does not further limit claim 1.

Claim 76 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 76 comprises a Markush group said to be tumors wherein

the tumor comprises leukemia. However, leukemia is not properly classified as a tumor and hence is outside the scope of the claims and should be deleted from the list of tumors.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 13-16, 18, 55, 56, 58, 59, 73, 74, 80 and 81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13, 14, 55 and 58 are vague and indefinite in that the metes and bounds of "cell comprises a hyperproliferative cell", "the hyperproliferative cell comprises a metastatic cell or a non-metastatic cancer cell" and "cell proliferative disorder comprises a metastatic or non-metastatic cancer" are unclear. It is unclear how a cell or disorder comprises a cell type such as a hyperproliferative cell. In this case, the claims are directed to "a cell" which cannot comprise another cell. In the case that the claims are drawn to a cell proliferative disorder, it is not clear how one would comprise a metastatic or non-metastatic disorder. A cell proliferative disorder is a condition that is found in for example a metastatic cell but it does not comprise the metastatic cell. It appears applicants intend that the cell is a hyperproliferative cell and the disorder is cancer.

Claims 15, 59, 73 and 74 are vague and indefinite in that the metes and bounds of the components of the Markush group are unclear. The claim by reciting "head or neck" can be reciting one of two ways the types of cells in which the treatment can occur. In the first

interpretation, it appears the cell is present (for example as recited in claim 15) in one of three sets of cells, 1) brain and head *or* 2) neck and all cell types up to muscle *or* 3) in the hematopoietic system. The second simply means that "head or neck" is a subgroup of cell types. However, the designation of "or" in the middle of the Markush group is unclear and would be better replaced with a comma for clarity.

Claims 80 and 81 are vague and indefinite in that the metes and bounds of the components of the Markush group are unclear. By recitation that the treatment comprises administering "an anti-tumor or immune enhancing treatment or agent" the Markush group as recited can be interpreted as 1) an anti-tumor 2) an immune enhancing treatment and 3) agent. It appears applicants may intend for administration of an agent or treatment that enhances the immune system of the subject or acts as an anti-tumor. If so, it would be remedial to amend the claim to clearly indicate all of the members of the group.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-10, 13-16, 18-28, 54-59, 61-63 and 69-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing glycogen to toxic levels in hyperproliferative cancer cells or tumor cells *in vitro* or *in vivo* or for the treatment of cancer or tumors by direct administration of nucleic acid encoding a glycogenic enzyme and expression of the glycogenic enzyme to increase glycogen to toxic levels, does not

reasonably provide enablement for any other embodiments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The instant invention is drawn to methods of increasing glycogen levels in a cell in methods of treating tumors or cancers to reach cytotoxic effects of glycogen.

2) **Scope of the invention**. The claimed invention is very broad in that the target cell is *any* cell encoding *any* gene product that increase the amount of glycogen in the cell by expression by *any* means so long as the expression leads to cytotoxic levels. Specifically, recited gene products are glycogenic enzymes such as a glycogen targeting subunit of PP-1. While the proteins listed as glycogenic enzymes are not technically enzymes, applicants indicate in that specification that this term is used to encompass all of the recited proteins by basis of their function in "increasing intracellular levels of glycogen regardless of the particular physiological or biochemical mechanism" (page 12, line 15-24). The methods are directed to *in vivo* methods of treating a person with a hyperproliferative cell (see page 32, line 13-18).

3) **State of Art**. The instant invention is directed to method of inhibiting growth and proliferation of hyperproliferative cells by achieving cytotoxic levels of glycogen. Glycogen has been in some types of cancer such as colon and rectum determined to be higher then surrounding tissues and hence the method relies on utilizing characteristic cancer metabolism. As well, the relationship between growth rate and malignancy of tumor has not been established. Fast growing carcinomas have lower glycogen levels then slow growing carcinomas. As well, glycogen levels was negatively correlated with tumor size (Takahashi et al, page 477, col 2, ¶ 1 and page 478, col 1, ¶ 2). At the time of filing, it was not apparent that this type of approach was successful (see e.g. Takahashi et al, page 477, col 2, ¶ 1).

4) **Number of working examples and guidance**. The specification teaches that target cells are hyperproliferative cells such as cells of a cell proliferative disorder- benign hyperplasia, metastatic and non-metastatic tumors and cancer cells. Means if increasing glycogen accumulation in the cell are through overexpression of glycogenic enzymes. In this way, Morphological changes that are associated with glycogen increase in a cell are cell swelling, increased numbers of lysosomes, increased size of lysosomes or a structural change in the lysosome, which are assayed by measuring cell proliferation or growth rat, survival time or viability. Applicants demonstrate in HeLa, LoVo (human colorectal cancer), MCF7 reduced viability with increased glycogen deposition after infection with a virus encoding Homo sapiens protein phosphatase 1, regulatory (inhibitor) subunit 3B (PPP1R3B) under control of a heat shock protein 70 translational enhancer, a WPRE enhancer. The effect is increased by addition of a cell cycle inhibitor, riscovitine.

5) **Unpredictability of the art**. The enablement of the instant invention has been assessed in light of the specification and the prior art available at the time of filing. "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b).

The claims are drawn broadly to *any* cell encoding *any* gene product that increase the amount of glycogen in the cell by expression by *any* means so long as the expression leads to cytotoxic levels. This means the claims are directed to any number of cells or disorders from which one must identify the level of glycogen necessary to lead to toxic effects for any number of cell types and then identify a gene product whose expression will lead to this increase in glycogen toxicity. There is a high degree of unpredictability to this invention. First, it is highly unpredictable that over-expression of a glycogenic enzyme can be accomplished by induction of the endogenous gene. As demonstrated in figure 4, enhanced expression is necessary to reduce cancer cell viability. Rather the method requires expression of the coding sequence of the enzyme by a promoter that is highly active or can be induced to be highly active. The specification teaches that this can be accomplished by introduction of a vector encoding a glycogenic enzyme into a hyperproliferative cell. The mechanism of action involves natural function of the glycogenic enzyme to produce glycogen that then accumulates to toxic levels. As well, the specification teaches that intracellular levels of glycogen that are toxic to the cell will vary in relative and absolute amounts depending on cell type, for example, muscle and liver have

greater amounts of intracellular glycogen and thus require higher levels of glycogen to reach toxic levels.

Secondly, applicants only demonstrate execution of the instant invention *in vitro* in HeLa, LoVo and MCF7 cells. Though not controlling, the lack of working examples, is, nevertheless, a factor to be considered in a case involving both physiological activity and an undeveloped art. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to substantiate them. *Ex parte Sudilovsky*, 21 USPQ2d 1702, 1705 (BPAI 1991); *In re Novak*, 134 USPA 335 (CCPA 1962); *In re Fouche*, 169 USPQ 429 (CCPA 1971). the lack of guidance exacerbates the highly unpredictable filed of gene therapy. The method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma et al (Verma and Somia, Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained expression". To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. In more advanced studies related to cancer, the art teaches "to bring about a desired therapeutic outcome. Reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle position in a tumour deposit." (Russell page 1165, col 2, ¶ 4-5).

6) **Summary**. For the reasons provided above, the invention lacks predictability the claims recite broadly that expression of *a gene product* in any cell by any means is used to reach toxic levels of glycogen. However, the efficacy of the method is based upon the ability of the gene product to reach supralevels of glycogen for which vector design and modulation of this level to reach therapeutic levels would require undue experimentation to determine. The lack of recited gene products other then exogenously introduced glycogenic enzymes and the lack of recited routes of the nucleic acid exacerbate the unpredictability of the art. In light of the art at the time of filing, the instant invention would require undue experimentation to perform the invention in humans and undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 8, 13-15 and 19-22 rejected under 35 U.S.C. 102(a) as regards claims 13-15, 19 and 102(e) as regards claims 1, 2 and 20-22 as being anticipated by Pennica et al (US/20020173461; see entire document).

Pennica et al teach a method of increasing glycogen levels in a cell by expressing Wnt in the cell (see e.g. ¶ 0163). Wnt controls glycogen accumulation by inhibiting glycogen synthase 3 kinase the net result of which is inherently the accumulation of glycogen as recited in claims 1, 2, 8 and 19-22. Absent evidence to the contrary the change in metabolic balance of glycogen will have toxic effects on the cells.

Claims 1, 2, 8-10 and 19-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Berman et al (JBC, 1998, pages 25421-25425; see entire document).

Berman et al teach a method of introducing PTG (PPP1R5) which is a glycogen targeting subunit into a cell on an adenoviral vector as recited in claim 1, 8-10 and 19-22. PTG increases accumulation of glycogen as recited in claim 2 to levels that increase glycogen levels and accumulation as demonstrated in figures 1 and 2. Absent evidence to the contrary, these levels are toxic to the cells as the metabolic balance of glycogen is altered.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Examiner
Art Unit 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER